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Case report

Primary pulmonary glomus tumor of uncertain malignant potential: A case report with literature review focusing on current concepts of malignancy grade estimation

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ABSTRACT

We report a 38-year-old woman with a left lung tumor presenting as obstructive pneumonia. Bronchoscopic examination revealed a polypoid tumor filling the left main bronchus. The tumor was partially resected by a snaring procedure for diagnostic purposes. Microscopic examination revealed a submucosal tumor located underneath normal bronchial epithelium. The tumor was composed of sheets of uniform oval to cuboidal cells encompassing numerous blood vessels. Immunohistochemically, the tumor cells exhibited smooth muscle markers, but were negative for neuroendocrine markers. The diagnosis of primary pulmonary glomus tumor was therefore made. Subsequent bronchoscopic intervention allowed us to pin-point the origin of the tumor: superior segmental $B^{6a/b}$. She underwent a left lower lobe superior segmental resection successfully. Glomus tumors are relatively rare soft tissue tumors, and those of bronchopulmonary origin are exceedingly rare clinical condition. Among primary lung tumors, the carcinoid tumor is a mimic of the glomus tumor, and differentiating these tumors is known to be difficult, especially using small biopsy samples. In the present case, a large tissue sample obtained by bronchoscopic snaring was quite useful for the correct preoperative diagnosis. Because of the disease rarity, malignancy grade estimation of visceral glomus tumors has not been clearly addressed. Recently, the histopathological diagnostic criteria for malignant glomus tumors was defined in the WHO classification of soft tissue and bone tumors 4th edition. Here we also reviewed the literature on primary bronchopulmonary glomus tumors with special attention to the current concept of malignancy grade estimation.

1. Introduction

Glomus tumors are relatively rare soft tissue tumors composed of cells that resemble the modified smooth muscle cells of the specialized form of arteriovenous anastomosis “glomus body” [1–4]. The most common site of the tumor is the subungual region; however, they occasionally occur in visceral organs such as airway tracts [1,2]. Primary glomus tumors of the lung are exceedingly rare, and the diagnostic and therapeutic strategies for this rare condition have not been well established. Here, we report a case of primary pulmonary glomus tumor that arose in a left segmental bronchus as a protruding polypoid mass with a clinical manifestation of obstructive pneumonia. In the present case, bronchoscopic intervention became a powerful tool not only for histological diagnosis but also for determining the proper operative procedure for the tumor. Ever since the criteria for the diagnosis of malignancy in glomus tumors was first established in 2001 [5], the malignancy estimation of visceral glomus tumors is a worrisome problem to be addressed because of the rarity of this condition. Recently, the criteria were modified and employed in the WHO classification of soft tissue and bone tumors 4th edition [4]. However, pulmonary glomus tumors diagnosed by the current WHO criteria have been scarcely reported. We also reviewed previous cases of primary bronchopulmonary glomus tumors in the literature, with special attention given to current diagnostic criteria.

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2. Case presentation

A 38-year old woman visited a local hospital with the chief complaint of high fever and was diagnosed with pneumonia. She had no history of smoking. She had a past medical history of bronchial asthma, but asthmatic symptoms had ceased for a long time. Although antibiotic treatment was properly initiated, her symptoms persisted. Chest CT examination revealed a left lower lobe atelectasis with a water density mass in the left bronchus (Fig. 1a). Bronchoscopic examination revealed a polypoid mass in the left main bronchus. She was suspected of having a primary bronchial tumor and was referred to our hospital for further examination. Physical examination revealed decreased air entry in the left lower lung. Routine hematological and chemical laboratory results were normal, except for a slight increase in CRP (1.0 mg/dl). Upon initial bronchoscopic examination, a polypoid tumor was observed that occluded nearly 90% of the lumen of the left main bronchus (Fig. 1b). For confirmation of the tumor type, a partial resection of the tumor was performed by bronchoscopic snaring. Postoperative chest X-ray revealed improvement of the atelectasis, and she was tentatively discharged. The partially resected surgical specimen consisted of tumor tissue that measured 1.5 cm in diameter (Fig. 1c). The tumor was well-circumscribed, firm, and tan in color (Fig. 1d). Microscopically, the tumor was located within the bronchial interstitial connective tissue covered by the bronchial epithelium with focal erosion. The tumor was composed of sheets of oval to cuboidal cells. Abundant vascular spaces were observed in the tumor, and some were surrounded by tumor cells (Fig. 2a). Blood vessels in the tumor were small to medium-sized, thin-walled, and some were dilated, resembling capillaries or venules. The tumor cells were uniformly monotonous with a centrally placed round nucleus and amphophilic to lightly eosinophilic cytoplasm (Fig. 2b). No necrosis, vascular invasion, obvious cellular atypia, or mitotic figures were observed. Immunohistochemically, the tumor cells exhibited cytoplasmic positivity for α-smooth muscle actin, calponin, and vimentin (Fig. 2c and d). Immunostaining was negative for desmin. The individual tumor cells were surrounded by positive staining for silver impregnation and anti-type IV collagen antibody, which showed an intricate chicken-wire pattern representing basement membrane material (Fig. 2e and f). No immunoreactivity was found for cytokeratin, CD34, CD31, S-100, CD56, chromogranin A, or synaptophysin (data not shown). Ki-67 immunolabeling was detected in approximately 3% of tumor cell nuclei. Histopathologically, the tumor was diagnosed as a

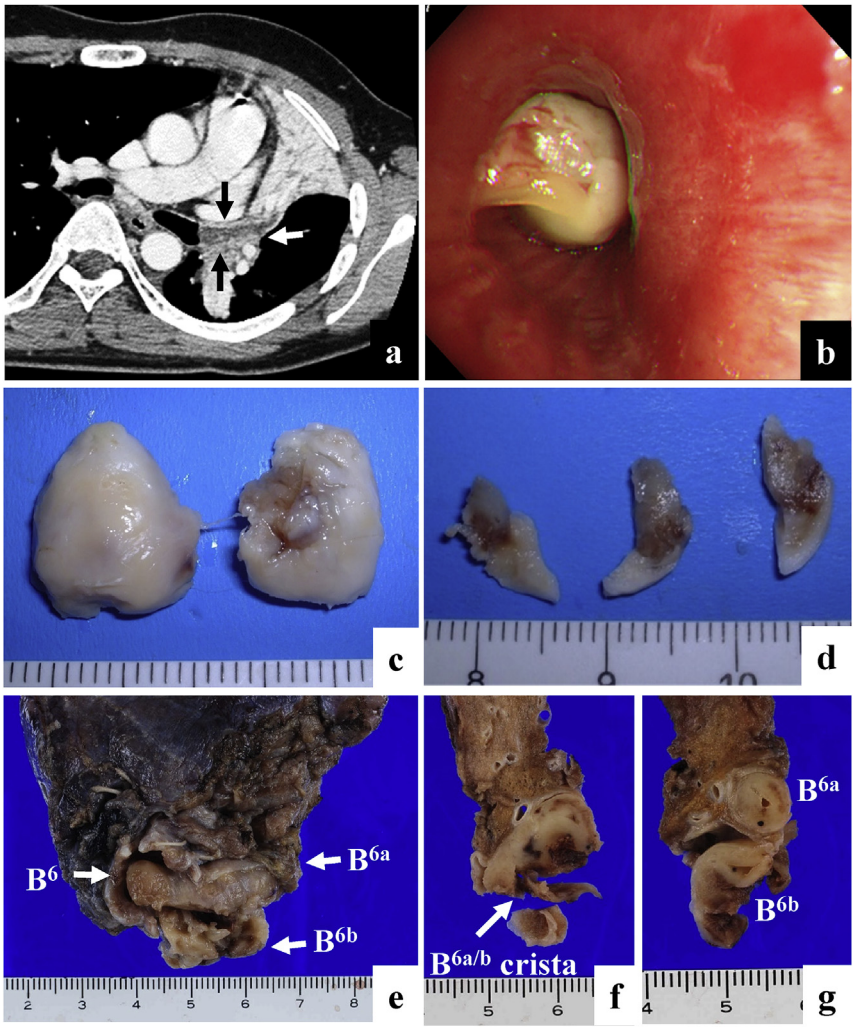

Fig. 1. Radiological, endoscopic, and macroscopic findings. (a) Contrast-enhanced chest CT reveals a water density mass in the left main bronchus (arrows). (b) Bronchoscopy shows a white polypoid mass filling the left main bronchial lumen. (c, d) The tip of the endobronchial tumor partially resected by endoscopic snaring procedure. The surface of the tumor is smooth, and the cut-surface is tan in color. (e–g) Formalin-fixed bronchopulmonary tissue obtained by left lower lobe segmental resection. A cylindrical mass arises from the superior segmental $B^{6a/b}$ crista and enlarged the lumen of B^{6}, B^{6a}, and B^{6b}.

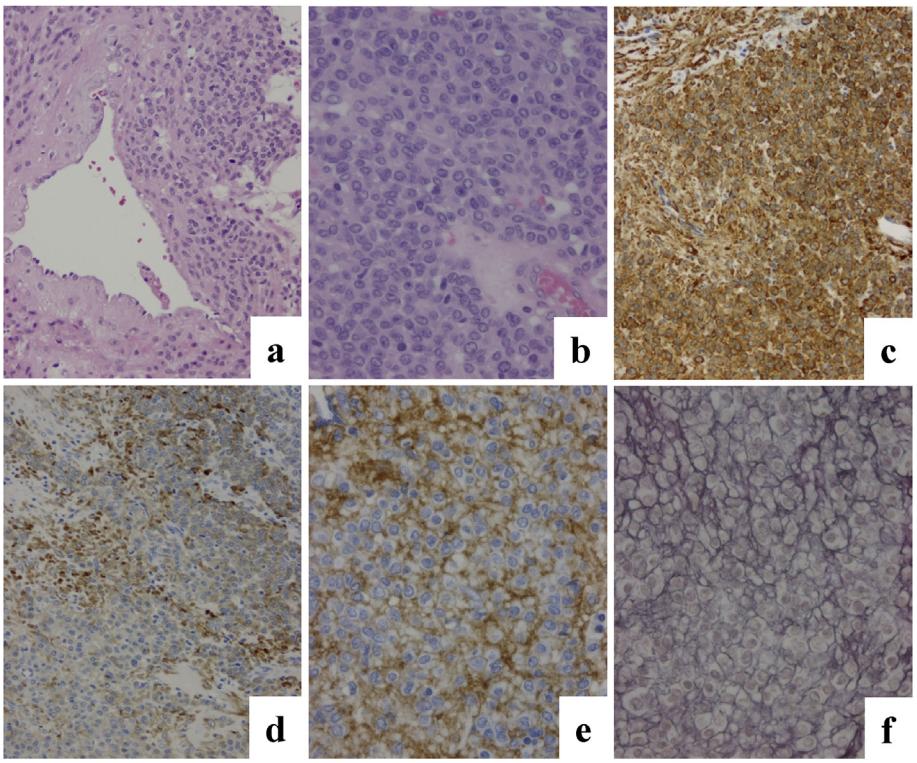

Fig. 2. Histological and immunohistochemical findings. (a) The tumor was composed of sheets of oval to cuboidal cells. Numerous vascular spaces are observed in the tumor. Characteristically, tumor cells are constituents of the neoplastic vascular walls. H&E stain, original magnification x200. (b) The tumor cells are bland and uniformly monotonous with a centrally placed round nucleus. There are no chromatin increment, obvious nucleoli, or mitotic figures. H&E stain, original magnification x400. (c) The tumor cells are strongly immunoreactive for anti-α-smooth muscle actin antibody. Original magnification x200. (d) A portion of tumor cells are also immunoreactive for anti-calponin antibody. Original magnification x200. (e) The individual tumor cell is surrounded by positive immunostaining for anti-type IV collagen antibody. Original magnification x400. (f) Silver impregnation shows an intricate chicken-wire pattern between tumor cells, representing basement membrane material. Original magnification x400.

classical glomus tumor. Two weeks later, she was re-admitted to our hospital because of total collapse of the left lung. A repeat bronchoscopic examination revealed total obstruction of the left main bronchus with bloody and fibrinous coagulation. After removal of the coagulative materials with biopsy forceps, the bronchial tumor was resected by a snaring procedure. Then, the origin of the tumor was confined to the bronchial mucosa of the left lower lobe superior segmental bronchus. One month later, she underwent a left lower lobe superior segmental resection. Grossly, the tumor was a firm cylindrical mass measuring 2.6 cm in length and 1.4 cm in diameter, which arose from the superior segmental $B^{6a/b}$ crista and filled and enlarged the lumen of B^{6}, B^{6a}, and B^{6b} (Fig. 1e–g). The proximal resection margin of the superior segmental bronchus was free of tumor. Histopathological examination of the resected specimen confirmed the preoperative diagnosis of a classical glomus tumor. In all sections, no necrosis, infiltrative growth, vascular invasion, conspicuous cellular atypia, increased mitotic activity, or atypical mitotic figures were observed. The patient had an uneventful postoperative course. She had no respiratory complaints and no recurrence of the tumor two years following tumor resection, and then she was lost to follow-up.

3. Discussion

Glomus tumors are distinctive mesenchymal neoplasms composed of cells that closely resemble the normal glomus body [1–4]. Glomus tumors are uncommon, with an estimated incidence of 1.6% in 500 consecutive soft tissue tumors [6]. The vast majority of glomus tumors occur in the dermis and subcutis of the extremities, with the single most common site of the subungual region of the finger; however, rare tumors have been reported in visceral organs [1,2]. Primary glomus tumors of the lung are exceedingly rare, with only 36 previously reported cases in the English literature (Table 1) [5,7–36]. Almost the same number of cases with primary tracheal glomus tumors have also been reported to date [37]. A survey of the literature shows that the primary bronchopulmonary glomus tumor usually occurred in adults, with the exception of a 9-year old female patient [5]. There is an obvious male predominance (26 out of 37), in sharp contrast with a striking female predominance (male to female ratio of 1:3) among patients with subungual lesions [1,2]. No causative relationship has yet been reported between smoking and tumorigenesis of glomus tumors. Primary pulmonary glomus tumors affected both bronchi and peripheral lung tissues including subpleural regions. In the bronchus, the tumor appeared as protruding polypoid masses, whereas it appeared as nodular lesions in the peripheral lung. The sizes of pulmonary glomus tumors tend to be larger than those of cutaneous glomus tumors with a typical tumor size of <1 cm [3,4]. Symptoms due to airway irritation and/or obstruction are common in bronchial glomus tumors, whereas peripherally arising glomus tumors are usually asymptomatic and found incidentally. The present case is a central (bronchial) type of glomus tumor of the lung presenting as pneumonia due to airway obstruction.

Histopathologically, there are two major diagnostic problems of primary pulmonary glomus tumors: first, the differential diagnosis of glomus tumors from other pulmonary tumors, and the second is the estimation of the malignant potential of this quite rare clinicopathological condition. In general, the items of differential diagnosis of cutaneal glomus tumors include adnexal tumors (especially hidradenoma) and less frequently intradermal nevi

Table 1
Summary of reported cases of primary bronchopulmonary glomus tumors.

Ref.	Age/sex	Presenting symptoms	Side	Location	Size (cm)	Biopsy diagnosis	Postoperative histological diagnosis	Metastasis; site	Treatment	Clinical outcome	Classification according to the WHO 3rd/4th ed.
[7]	67/M	Epigastralgia	L	Lower lobe, subpleural	6.5	N/A	GT	No	Lobectomy	FOD at 9 months	MGT/GTUMP
[8]	34/M	ASX	R	Upper lobe	2.0	N/A	GT	No	Lobectomy	N/A	GTUMP/GTUMP
[9]	50/M	ASX	R	Subpleural	1.1	Not performed	GT	No	Wedge resection	N/A	GTUMP/GTUMP
[9]	41/M	ASX	R	Lower lobe, peripheral	1.5	Not performed	GT	No	Wedge resection	FOD at 47 months	GTUMP/GTUMP
[10]	20/M	Pneumothorax	L	Main bronchus	1.4	Carcinoid	GT	No	Sleeve resection	FOD at 9 months	GTUMP/GTUMP
[10]	65/F	ASX	R	Infrahilar	3.0	Not performed	GT	No	Wedge resection	FOD at 60 months	MGT/GTUMP
[10]	40/M	ASX	R	Lower lobe, subpleural	1.1	Hemangiopericytoma	GT	No	Lobectomy	FOD at 6 months	GTUMP/GTUMP
[10]	69/M	Hemoptysis	R	Upper lobe	9.5	Not performed	Glomangiosarcoma	Lung, Mediastinum, Brain, Liver, Skin	Lobectomy; chemotherapy	DOD at 17 months	MGT/MGT
[5]	38/M	N/A	N/A	Lung	3.8	N/A	Glomangiosarcoma	N/A	N/A	N/A	MGT/MGT
[5]	9/F	N/A	N/A	Lung	4.5	N/A	Glomangiosarcoma	GI tract	N/A	AWD at 60 months	MGTMGT
[11]	48/M	Hemosputum	L	Main bronchus	0.7	GT	GT	No	Wedge resection	FOD at 3 months	GTUMP/GTUMP
[12]	29/F	Cough, dyspnea, chest pain	L	Main bronchus	1.5	Carcinoid tumor	GT	No	Bronchotomy plus mass extirpation	FOD at 17 months	GTUMP/GTUMP
[13]	53/M	Cough	R	Basal bronchus	2.5	Degenerated atypical cells	Glomangiosarcoma	No	Lobectomy	FOD at 23 months	MGT/MGT
[14]	29/M	Chest discomfort	R	Main bronchus	3.0	Adenoma	GT of undetermined malignant potential	No	Sleeve upper lobectomy with node dissection	N/A	MGT/GTUMP
[15]	40/M	Fever, cough, chest pain	R	Main bronchus	0.9	Not performed	GT	No	Endoscopic removal	FOD at 1 month	GTUMP/GTUMP
[16]	50/M	ASX	R	Upper lobe	4.0	N/A	GT	No	Lobectomy	N/A	MGT/GTUMP
[17]	37/M	Cough	R	Bronchus intermedius	N/A	GT	Not obtained	No	Laser coagulation followed by cryotherapy	FOD at 3 months	N/D
[18]	67/M	Cough	R	Superior bronchial trunk	0.8	Typical carcinoid	GT	No	Segmental resection	N/A	GTUMP/GTUMP
[19]	64/M	ASX	L	Lower lobe	3.5	Not performed	Glomangioma	No	Tumor removal	N/A	MGT/GTUMP
[20]	56/F	Hemoptysis	R	Lower lobe	5.5	Not diagnostic	Glomangiomyoma	No	Lobectomy	N/A	MGT/GTUMP
[21]	34/M	Cough	R	Bronchus intermedius	2.3	Typical carcinoid	GT	No	Sleeve resection	N/A	MGT/GTUMP
[22]	55/M	ASX	R	Upper lobe	1.1	N/A	GT	No	Lobectomy	N/A	GTUMP/GTUMP
[23]	69/M	Hemoptysis	R	Main bronchus	2.0	Angiomatous lesion	GT	No	N/A	N/A	GTUMP/GTUMP
[24]	21/F	ASX	L	Upper lobe, parahilar	2.5	N/A	GT	No	Lobectomy	N/A	MGT/GTUMP
[25]	39/M	Cough	L	Main bronchus	2.5	GT	GT	No	Endoscopic resection	FOD at 72 months	MGT/GTUMP
[26]	74/M	Cough, dyspnea, chest pain	R	Upper lobe, parahilar	3.4	GT	Glomangiosarcoma	No	Lobectomy with node dissection	FOD at 12 months	MGT/MGT
[27]	late 30s/M	Hemosputum	R	Bronchus intermedius	1.5	Carcinoid, suspected	GT	No	Sleeve lobectomy	FOD at 10 months	GTUMP/GTUMP
[28]	39/M	ASX	L	Upper lobe	N/A	Neuroendocrine tumor	Glomangioma	No	Lobectomy with node dissection	FOD at 51 months	N/D
[29]	62/M	Hemoptysis	L	Main bronchus	1.6	GT	GT	No	Sleeve lobectomy	FOD at 30 months	GTUMP/GTUMP
[30]	35/F	Hemoptysis	L	Hilum	N/A	Glomangiosarcoma	Glomangiosarcoma	Lymph node, Lung	Pneumonectomy with node dissection	N/A	MGT/MGT
[31]	43/F	ASX	R	Upper lobe, peripheral	2.0	Sclerosing hemangioma	GT	No	Thoracoscopic lung resection	FOD at 6 months	GTUMP/GTUMP
[32]	28/M	Hyperpyrexia, anemia	R	Upper lobe	3.0	Not performed	Low-grade MGT	No	Lobectomy	FOD at 12 months	MGT/Suspicion of GTUMP
[33]	60/F		L		2.5	MGT	Not obtained		Not performed		MGT/MGT

Table 1 (*continued*)

Ref.	Age/sex	Presenting symptoms	Side	Location	Size (cm)	Biopsy diagnosis	Postoperative histological diagnosis	Metastasis; site	Treatment	Clinical outcome	Classification according to the WHO 3rd/4th ed.
		Cough, hemoptysis		Upper lobe, parahilar				Lymph node, GI tract, Spleen, Adrenal gland		DOD within a few months	
[34]	49/M	Cough, dyspnea, chest pain	R	Lower lobe	3.0	Not performed	GTUMP	No	Wedge resection	N/A	MGT/GTUMP
[35]	59/F	Cough, hemoptysis	L&R	Multiple	2.5	MGT	Not obtained	Lymph node, Lung, GI tract, Spleen	Not performed	DOD within 20 weeks	MGT/MGT
[36]	66/F	ASX	R	Middle lobe	4.5	Not performed	MGT	No	Lobectomy	FOD at 13 months	MGT/ Suspicion of GTUMP
*	38/F	Fever	L	Lower lobe, B^6	2.6	GT	GTUMP	No	Segmentectomy	FOD at 24 months	MGT/GTUMP

AWD, alive with disease; ASX, asymptomatic; DOD, died of disease, DOOD, died of other disease; F, female; FOD, free of disease; GI, gastrointestinal; GT, glomus tumor; GTUMP, glomus tumor of uncertain malignant potential; L, left; M, male; MGT, malignant glomus tumor; N/A, not available; N/D, not determinable because of undetailed histological information; R, right; *, our case.

[1,2]. In the rare condition of bronchopulmonary glomus tumors, however, the most important differential diagnosis would be a carcinoid tumor from the viewpoint of pathologists. A considerable number of primary pulmonary glomus tumors were initially misdiagnosed as carcinoid tumors based on the preoperative biopsy or intraoperative frozen section examinations [10,12,18,21,27,28]. Carcinoid tumors bear some clinical, radiological, and histopathological similarities to glomus tumors [15]. On the basis of radiological findings alone, they are difficult to distinguish because both of them appear as a well-delineated round mass by contrast enhancement [16]. Histologically, uniformly monotonous tumor cells having bland round nuclei are common features of both, but the appearance of tumor cell nuclei is different between the two tumor entities. Glomus tumors lack the characteristic salt and pepper appearance of nuclear chromatin distribution typical for carcinoid tumors. Although both glomus tumors and carcinoid tumors are rich in blood vessels, it is important to note the differences in vasculature between these tumors. In carcinoid tumors, capillaries within delicate fibrous septa separate each tumor cell nest showing an organoid arrangement typical to neuroendocrine tumors; conversely, glomus tumor cells are constituents of neoplastic vascular walls resembling a normal glomus body. Immunohistochemically, positivity for cytoplasmic smooth muscle markers and pericellular basement membrane constituents is a reliable marker for glomus tumors. Neuroendocrine markers are always positive in carcinoid tumors, whereas they are negative in glomus tumors. Thus, immunohistochemical examination definitively differentiates these two entities, and recognition of the aforementioned cytological and vascular structural features is the most important point for planning an immunohistochemical evaluation.

Estimation of the malignant potential of bronchopulmonary glomus tumors is the other problem to be addressed. Indeed, most glomus tumors are benign and can be treated adequately by simple excision. However, glomus tumors showing histological atypia have been recognized, and furthermore, fatal cases with distant metastases are occasionally reported, comprising less than 1% of all glomus tumors [3]. For primary bronchopulmonary glomus tumors, 10 cases with malignancy have been previously reported [5,10,13,26,30,32,33,35,36]. Criteria for the diagnosis of malignancy in glomus tumors was proposed by Folpe et al. for the first time in 2001 [5]. The criteria were introduced in a textbook of soft tissue tumors by Enzinger and Weiss [1] and employed in the WHO classification of soft tissue and bone tumors, 3rd edition [3]. In the criteria, the diagnosis of “malignant glomus tumor” should be reserved for tumors showing the following: 1) large size (>2 cm) and deep location; 2) atypical mitotic figures; or 3) marked atypia with mitotic activity. According to the criteria, the majority of visceral glomus tumors could be diagnosed as “malignant” because of their consistent “deep” location and relatively large sizes. In the literature, however, 10 out of 19 cases of bronchopulmonary glomus tumors with sizes of >2.0 cm did not show histologically atypical features or clinically malignant behavior. Because the first criterion was elaborated mainly based on a large number of atypical glomus tumors of the skin, whether this criterion was applicable to visceral glomus tumors remained uncertain [14]. Currently, growing evidence has shown that most of the large and deeply located glomus tumors behave in a clinically benign fashion; therefore, the first diagnostic criterion was modified, and these lesions are now considered glomus tumors of uncertain malignant potential [2,4]. Previous and current diagnostic criteria of glomus tumors with atypical features proposed by Folpe et al. are comparatively shown in Tables 2 and 3. Briefly, glomus tumors of >2 cm in size with a deep location were previously diagnosed as malignant but are now categorized as having uncertain malignant potential. Visceral glomus tumors are essentially considered bearing uncertain malignant potential because of their deep location. However, malignancies are defined solely by histological findings in the current criteria. In our case, the tumor is 2.6 cm in maximal diameter, but neither mitotic figures nor an obvious nuclear atypia was observed. Our case is therefore defined as a glomus tumor of uncertain malignant potential, according to the current diagnostic criteria [2,4]. The tumor grew cylindrically in the bronchial lumen with no infiltrative growth. There was no necrosis. Ki-67 immunolabeling was found in only approximately 3% of tumor cells. All of these findings suggested the probable benign nature of the tumor. A conservative surgery was therefore considered feasible. Our repeated bronchoscopic intervention allowed us to identify the origin of the tumor, thus opening a door for limited resection. Without the repeated interventions, the patient would have required at least a lobectomy. To date, the follow-up of glomus tumors of uncertain malignant potential has been good, but the number of cases is small and the follow-up period is short. Because it is still unclear whether large visceral glomus tumors are truly benign or potentially malignant indolent tumors, close postoperative follow-up is warranted.

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Table 2
WHO classification of glomus tumors with atypical features.

WHO 3rd edition (2002)	WHO 4th edition (2013)
Malignant glomus tumors	
1) Size >2 cm and subfascial or visceral location or	1) Marked nuclear atypia and any level of mitotic activity or
2) Marked nuclear atypia and any level of mitotic activity or	2) Atypical mitotic figures
3) Atypical mitotic figures	
Glomus tumors of uncertain malignant potential	
Not fulfilling criteria for malignancy, but having at least one atypical feature other than nuclear pleomorphism	Not fulfilling criteria for malignancy, but having at least one atypical feature other than nuclear pleomorphism
Symplastic glomus tumors	
Striking nuclear atypia in the absence of any other worrisome feature (e.g., large size, deep location, mitotic activity, necrosis)	Striking nuclear atypia in the absence of any other features indicative of negative outcome (e.g., large size, deep location, mitotic activity, necrosis)

Table 3
Classification of glomus tumors with atypical features in *Enzinger and Weiss's Soft Tissue Tumors*.

5th edition (2008)	6th edition (2014)
Malignant glomus tumors	
1) Marked atypia + mitotic activity (5 > 50 HPF) or	1) Marked atypia + mitotic activity (5 > 50 HPF) or
2) Atypical mitotic figures or	2) Atypical mitotic figures
3) Large size (>2 cm) + deep location	
Glomus tumors of uncertain malignant potential	
1) Superficial location + high mitotic activity (>5/50 HPF) or	1) Superficial location + mitotic activity (5 > 50 HPF) or
2) Large size only or	2) Large size (>2 cm) and/or deep location
3) Deep location only	
Symplastic glomus tumors	
Lacks criteria for malignant glomus tumor and marked nuclear atypia only	Lacks criteria for malignant glomus tumor and marked nuclear atypia only

agencies in the public, commercial, or not-for-profit sectors.

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